

0. Abstract.

Uveal melanoma is a life-threatening disease for which there is as yet no curative treatment. Once metastasis has occurred, the survival rate is very low. Little is known so far about the genetics underlying this malignancy. In particular, the relevance of mitogen-activated protein kinase (MAPK) pathway in the development of uveal melanomas remains unclear. While BRAF and NRAS mutations are a common event both in benign and malignant melanocytic neoplasms, uveal melanoma and other melanocytic neoplasms without epithelial association harbor no equivalent oncogenic events.

This report presents novel data following the discovery of somatic mutations in the heterotrimeric G protein alpha q subunit (GNAQ), found in 44% of uveal melanomas, 83% of blue nevi, and 50% of melanomas arising within blue nevi. GNAQ^{Q209L} activates the MAPK pathway, with levels of ERK phosphorylation comparable to a NRAS^{Q61R} - mutant condition. We showed that primary normal human melanocytes expressing GNAQ^{Q209L} exhibit phenotypical changes in cellular and nuclear morphology. Furthermore, introducing GNAQ^{Q209L} to immortalized melanocytes triggered anchorage-independent growth.

Conversely, silencing GNAQ^{Q209L} by siRNA reduced colony formation in soft-agar and induced apoptosis in uveal melanoma cell lines carrying a GNAQ mutation. Investigating its downstream signaling, the Protein kinase C (PKC) family was identified as potential therapeutic targets. Phospho-PKC μ (P-PKD) and total PKC ϵ levels were found to be elevated in mutant-GNAQ expressing cells. Preliminary experiments using specific PKC inhibitors failed to reduce levels of P-PKD or induce apoptosis. Still, as siRNA against GNAQ^{Q209L} significantly decreased levels of P-PKD, and as notably high levels of P-PKD and total PKC ϵ were detected in patient-derived uveal melanoma cell lines carrying a GNAQ mutation, further investigation of these proteins as therapeutic targets is still warranted.

Also, we were able to show that BRAF protein levels are higher in uveal melanoma cell lines with mutant GNAQ as measured by Western blot – while the analysis of a public data base suggests that BRAF expression levels are indeed high in uveal melanoma patients with GNAQ mutation.

Further experiments will be necessary to draw any final conclusion, but the pathway downstream of oncogenic GNAQ certainly bears important therapeutic potential, while the purport research could find translation into clinics relatively fast.